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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,014	01/03/2001	Jeff Nordstrom	260/056	2763

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 07/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/754,014	Applicant(s) NORDSTROM ET AL.	
	Examiner Daniel Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-16 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Cl im(s) *1-4,8,9,13 and 45-49* is/are rejected.

7)☒ Cl im(s) *5-7,10-12 and 14-16* is/are objected to.

8)☐ Cla m(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ Th d awing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ Th proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity un . 35 U.S.C. §§ 119 and 120

13)☐ A owledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ l b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* Se e attached detailed Office action for a list of the certified copies not received.

14)☒ Ac owledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Ac owledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Inform Dis sure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is a response to the Amendment and Response to Restriction Requirement filed April 30, 2002. Claims 8 and 9, as filed, amended claims 1-7 and 10-16, and new claims 45-49 are pending in the Application. This application, filed January 3, 2001, is a Continuation of Application number 08/948,958, filed October 10, 1997, which claims benefit of 60/028,687, filed October 18, 1996.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-16, in Paper No. 8 is acknowledged.

Claims 17-44 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Specification

The disclosure is objected to because of the following informalities: the specification and claims contain nucleotide and amino acid sequence that is not identified by SEQ ID numbers. Appropriate correction is required. In the interest of compact prosecution, the Examiner is assuming that the claims are drawn the following sequences: claims 5, 10 and 14 to nucleotides 1-9 of SEQ ID NO:10; claims 6, 11 and 15 to nucleotides 16-22 of SEQ ID NO:10; and claims 7, 12 and 15 to nucleotides 25-45 of SEQ ID NO:10.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 45-47 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection. The claims are drawn to plasmids comprising a 5'-untranslated region that is "about 54 nucleotides long" or a synthetic intron that is "about 118 nucleotides long". The disclosure as originally filed, however, describes in definite terms only a 5'-untranslated region "designed to be moderate in length (54 nucleotides)" (page 30, lines 24-25 of the specification) and a synthetic intron 118 nucleotides in length (page 34, line 1 of the specification). Because the disclosure as originally filed does not

recite the definite limitation "about", one of ordinary skill in the art would not conclude that Applicant was in possession of the full scope of the invention as claimed at the time of filing.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 45, 46, 48 and 49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, and claims 3 and 4 as they depend from claim 2, are drawn to plasmids comprising first and second 5'-untranslated regions that are deficient in G, but rich in C and A residues. In addition, Claim 4 recites the further limitation that the 5'-untranslated region is lacking in AT-rich sequences. The claims are indefinite because the disclosure fails to provide concrete metes and bounds for the limitations "deficient", "rich" and "lacking". The limitation "lacking in AT-rich sequences" is particularly vague because it refers to subsequences within the 5'-untranslated region of unspecified length. The limitations appear in the specification beginning on page 30, final paragraph and continuing on page 31 through line 3. The disclosure does not however provide an objective measure by which one can determine when these limitations are met. It would appear from the disclosure and the cited art, especially Jansen et al. (IDS #BN) and Kozak (IDS #BS), that the purpose of these limitations is to optimize translation of the encoded proteins by reducing secondary structure in the 5'-untranslated region and by stabilizing the transcript. Although this still does provide a definite limitation, if the limitations were allowed one could assume that they are met, to a sufficient degree, by any 5'-untranslated

region that provides high-level expression of the encoded protein. Because most expression vectors known in the art are designed to provide high-level expression of the gene of interest, it can be further assumed that any of these vectors, including the vectors applied below against the base claims from which these claims depend meet the limitations.

It would appear that the dependence of claims 45 and 46, which depend from claims 1 and 8 respectively, is reversed. Claim 45 recites limitations drawn to a single synthetic intron, while the plasmid of claim 1 comprises two introns, and claim 46 recites limitations drawn to first and second synthetic introns, while the plasmid of claim 8 comprises a single intron. As written, there is unclear, or insufficient, antecedent bases for the intron or introns in the base claims. In the interest of compact prosecution the claims have been examined on the merits with the assumption that claim 45 should depend from claim 8 and claim 46 should depend from claim 1.

Claims 48 and 49 are drawn to the synthetic intron OPTIVS8B. On page 32, line 8, the exemplary synthetic intron is referred to as "OPTIVS8" and the structure of OPTIVS8 is provided. Thereafter, the synthetic intron is always referred to as "OPTIVS8B" in both the specification and the claims. The specification does not clearly link the structure on page 32 with the claimed OPTIVS8B, however, and therefore does not provide a definite limitation. It appears that Applicant's intention is that the structure provided on page 32 of the specification is that of OPTIVS8B, which has unintentionally been mislabeled OPTIVIS8. Therefore the claims have been examined on the merits with the assumption that they are drawn to plasmids comprising the intron structure disclosed on page 32 of the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim1 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Mascarenhas (IDS #CS) or Petitclerc (1995) *J. Biotechnol* 40:169-178 in view of any one of Mulvihill et al. (IDS #AC), Carrano et al. (IDS AD) or Ligon et al. (IDS AE).

The claim is drawn to an eukaryotic expression vector comprising two transcription units, each of said transcription units comprising, in order from 5' to 3': a transcriptional control sequence; a 5'-untranslated region comprising a synthetic intron; a coding sequence; and a 3'-untranslated region/poly (A) signal.

Mascarenhas and Petitclerc teach all of the components of the transcription unit described above (see especially Mascarenhas page 914, Figure 1 and Petitclerc page 171, Figure 1). Mascarenhas teaches transcription units composed of control sequences from CMV (cauliflower

mosaic virus), 5' UTR, synthetic introns of varying compositions, coding sequences and a 3' UTR. Petitclerc teaches transcription units composed of control sequences from human cytomegalovirus (hCMV), 5' UTR, a synthetic hybrid intron containing an adenovirus splice donor and an immunoglobulin G splice acceptor, a bovine growth hormone coding sequence, and 3' UTR.

Mulvihill teaches co-expression of genes in eukaryotic cells (columns 7-11). They teach the coordinated expression of a gene of interest (see column 6) with a gene encoding a processing and/or stabilizing protein(s). They too describe transcription units with some of the recited elements or components. They also teach that the transcription units for both the gene of interest and the gene encoding a processing and/or stabilizing protein(s) may be on the same vector and that these genes may be controlled by the same or different promoters. At the top of column 11, they teach that the expression units (transcription units) may be on a single expression vector.

Carrano teaches components or elements necessary for gene expression (see especially column 6). They teach the basic elements (paragraph 1), provide examples of elements that are suitable, such as the control sequences from CMV, and polyadenylation signals. And, Carrano teaches certain embodiments wherein the plasmid may contain more than one expression unit (see especially the top of column 36).

Ligon teaches methods of expressing multiple genes, comprising the biosynthetic pathway for antipathogenic agents, in plants. They teach expression cassettes (transcription units) as well as the desirability to put more than one expression cassette on a transformation

vector, such as a plasmid, to reduce the number of plant transformations (see especially column 69).

Mascarenhas or Petitclerc teach all of the elements or components of the transcription unit and demonstrate or describe the functions of the recited elements. They teach enhanced expression using a synthetic intron and have incorporated this element for this purpose in a transcription unit. They further teach the recited order of the elements. They do not teach vectors with more than one transcription unit.

Mulvihill, Carrano, and Ligon each teach plasmids with multiple transcription or expression units or expression cassettes for coordinated expression of multiple coding sequences. These references illustrate that, prior to the filing date of the instant application, making expression vectors with multiple transcription units for the coordinated expression of genes in eukaryotic cells was well known.

One of ordinary skill in the art would have been motivated to use the elements taught by Mascarenhas or Petitclerc in a transcription unit to enhance the expression of a gene of interest. The ordinary artisan would have been further motivated to use transcription units patterned after the teachings of Mascarenhas or Petitclerc in polycistronic expression vectors, exemplified by Mulvihill, Carrano or Ligon, to obtain enhanced expression of coding sequences in a coordinated fashion. The latter three references teach the desirability of creating vectors with multiple transcription units or expression cassettes to obtain coordinated expression of genes. The prior art teaches that configuring plasmids with multiple transcription units or expression cassettes reduces the number of transformations for host cells and coordinates expression of "related" genes. Genes may be related as being part of a biosynthetic pathway, as exemplified by Ligon, or

have a relationship as described by Mulvihill, wherein the one cassette or unit encodes for the product of interest, while the other cassettes or units encode for products which stabilize or process or augment the activity or function of the product of interest. The ordinary artisan would have had an expectation of success because of the teachings of the prior art, which demonstrate that synthetic introns increase or enhance expression of coding sequences and the existence of polycistronic plasmids which bring about coordinated expression of multiple sequences in eukaryotic cells. Thus, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mascarenhas or Petitclerc in view of Mulvihill, Carrano or Ligon, as applied to clam 1 above and in further view of Zitvogel (IDS CQ).

Claim 8 is drawn to a eukaryotic expression vector comprising an intron having variable splicing, a first coding sequence and a second coding sequence. Claim 9 is drawn to the plasmid of claim 8 further comprising: a transcriptional control sequence linked with a first and a second coding sequence; a 5' UT region; an intron 5' to the first coding sequence; an alternative splice site 3' to said first coding sequence and 5' to said second coding sequence; and a 3'-UT region/poly (A) signal.

As described above, Mascarenhas, Petitclerc, Mulvihill, Carrano and Ligon teach all of the limitations of the expression units and a vector comprising two coding sequences. Although they teach a plasmid comprising an intron, they do not teach an intron capable of alternative splicing. Fischer teaches that prokaryotic cloning vehicles (plasmids) are modified to include

sequences which facilitate the expression of genes in eukaryotic cells (see especially column 5). They teach elements such as promoters, alternative splice sites and polyadenylation signals are all necessary for gene expression in eukaryotic cells. This reference illustrates that as of 1989 (the filing date of the parent application for the patent), the elements necessary for gene expression in eukaryotic cells was well known. Thus, the ordinary artisan would have been motivated to construct a polycistronic plasmid that comprises an alternative splice site between two coding regions as a means by which to obtain expression of both coding regions and the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claim13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dirks et al. (IDS #CT) in view of Rautmann and Breathnach (1985) *Nature* 315:169-178.

The claim is drawn to a eukaryotic expression vector comprising: a transcriptional control sequence transcriptionally linked with a first coding sequence, an IRES sequence, a second coding sequence and a 3'-UT region/poly (A) signal, wherein said IRES sequence is between said first and second coding sequences; and a synthetic intron between said transcriptional control sequence and said first coding sequence.

Dirks teaches a dicistronic plasmid for the expression of genes in eukaryotic cells (see especially Figure 1). Their teachings show a plasmid which has a transcriptional control sequence linked to a first coding sequence followed by an IRES sequence, then a second coding sequence and a 3'-UT region. The plasmid also features an intron comprising splice donor and acceptor sites from SV40 Vp2 between the transcriptional control sequence and the first coding

sequence. Dirks does not explicitly teach a synthetic intron. Rautmann teaches expression units comprising synthetic introns (see especially Figure 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Dirks to include the synthetic intron of Rautmann according to the teachings of the instant application. The teachings of Dirks and Rautmann can be easily combined by simply substituting the intron taught by Rautmann for the intron of the expression vector taught by Dirks. Motivation to combine these teachings comes from Rautmann, who teaches a significant enhancement of splicing with the introduction of a globin branchpoint sequence into the intron. Because Dirks does not teach an intron comprising a branchpoint sequence, the skilled artisan would be motivated to use the synthetic intron taught by Rautmann. One would have a reasonable expectation of success in combining these teachings, as Rautmann demonstrates the effectiveness of his intron in mammalian cells and Dirks describes a mammalian expression system.

Allowable Subject Matter

Claims 5-7, 10-12 and 14-16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
July 24, 2002

JAMES KETTER
PRIMARY EXAMINER